

I. A SEARCH FOR ANTIMETABOLITES RELATED TO
THE AMINO ACIDS

II. A SYNTHESIS OF *dl*-3,4-DIHYDROXY-
PHENYLALANINE

BY

FREDERICK JOHN PILGRIM

B.S., Rensselaer Polytechnic Institute, 1939

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AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
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PART ONE

A SEARCH FOR ANTIMETABOLITES RELATED TO THE AMINO ACIDS

INTRODUCTION

The therapeutic properties of sulfanilamide and the sulfa drugs have been attributed to the close structural relationship which exists between the sulfa drugs and the metabolite, *p*-aminobenzoic acid (PABA). The sulfa drugs are believed to interfere with the role of PABA in the metabolism of bacteria and, in so doing, to exert their bactericidal effects. In recent years a large number of structural analogs of other metabolites have been studied to determine whether a similar antagonistic relationship exists.

The present work was undertaken in an effort to prepare certain structural analogs of essential amino acids, tryptophan in particular, which might function as antimetabolites.

DISCUSSION OF RESULTS

Two structural analogs of tryptophan have been prepared as potential antimetabolites. *dl*-Homotryptophan [α -amino- γ -(3-indole)-butyric acid] was synthesized *via* the sequence: indole, tryptophol, β -(3-indole)-ethyl bromide, ethyl α -acetamino- α -carbethoxy- γ -(3-indole)-butyrate, α -acetamino- α -carboxy- γ -(3-indole)-butyric acid, α -acetamino- γ -(3-indole)-butyric acid, *dl*-homotryptophan.

dl-6-Methyltryptophan [α -amino- β -[3-(6-methyl)-indole]-propionic acid] was synthesized *via* the sequence: *p*-xylene, 2-nitro-1,4-dimethylbenzene, 2-nitro-4-methylphenylpyruvic acid, 6-methylindole, 6-methyl-3-(dimethylaminomethyl)-indole (6-methylgramine), ethyl α -acetamino- α -cyano- β -[3-(6-methyl)indole]-propionate, *dl*-6-methyltryptophan.

New syntheses of 3-indoleacetic acid and tryptophol were developed. 3-Indoleacetic acid (heteroauxin) was prepared in

90% yield when gramine was treated with an alcoholic solution of sodium cyanide and the resulting 3-indoleacetonitrile was saponified, without isolation, to the acid. Tryptophol [β -(3-indole)-ethanol] was prepared by the lithium aluminum hydride reduction of 3-indoleacetic acid.

A study was initiated which had as its objective the synthesis of a tryptophan analog in which the benzene ring of the indole nucleus is replaced by a thiophene ring. Although the study was not completed there was sufficient evidence to indicate that a feasible synthetic procedure had been initiated *via* the sequence: 3-methylthiophene, 3-thenyl bromide, 3-thenyl cyanide, 2-nitro-3-thenyl cyanide, and finally simultaneous reduction and ring-closure to the desired indole analog.

Preliminary investigations of two possible syntheses of α -aminosulfonamides related to the α -amino acids have been carried out. One procedure consists in the acylation of the salt of an α -aminosulfonic acid (prepared from the bisulfite addition product of an aldehyde), followed by conversion of the sulfonate group to the sulfonyl chloride and reaction with ammonia to give an acylaminosulfonamide. This route was successful in the preparation of carbobenzoxy α -aminoisobutane sulfonamide although in low yield. Removal of the carbobenzoxy group was not studied. The alternative preparation considered involved the degradation of an α -amino acid by treatment of the silver salt of the N-phthalyl derivative with bromine, replacement of the bromine atom of the product by a sulfonate group, conversion of the N-phthalimido sulfonate to the sulfonyl chloride and sulfonamide, and removal of the phthalyl group with hydrazine. In the application to N-phthalyl phenylalanine the reaction of the silver salt with bromine failed, and the route was abandoned.

PART TWO

A SYNTHESIS OF *dl*-3,4-DIHYDROXYPHENYLALANINE

INTRODUCTION

3,4-Dihydroxyphenylalanine (dopa) has been postulated

as an intermediate in the biological transformation of tyrosine to epinephrine and as an intermediate in the biological synthesis of melanin.

The present work was undertaken in an effort to develop a new synthesis which might be more readily adaptable to large scale operations than the previously reported syntheses.

DISCUSSION OF RESULTS

Dopa hydriodide was prepared by the following reaction sequence: vanillin, veratraldehyde, veratryl alcohol, veratryl chloride, ethyl α -acetamino- α -carbethoxy- β -(3,4-dimethoxyphenyl)-propionate, α -acetamino- α -carboxy- β -(3,4-dimethoxyphenyl)-propionic acid, α -acetamino- β -(3,4-dimethoxyphenyl)-propionic acid, 3,4-dimethoxyphenylalanine, *dl*-3,4-dihydroxyphenylalanine hydriodide (dopa hydriodide). The hydriodide is quite stable, in comparison to the easily oxidized dopa. Preliminary work indicated that the conversion of the hydriodide to dopa could be best effected by silver oxide in a solution saturated with sulfur dioxide.

Another preparation of 3,4-dimethoxyphenylalanine, an intermediate in the above reaction sequence, was carried out which involved the condensation of veratryl chloride with sodiumacetaminocyanoacetic ester and basic hydrolysis of the resulting condensation product. The two preparations of 3,4-dimethoxyphenylalanine were equally satisfactory. Acid hydrolysis of the intermediate condensation products appeared to be undesirable due to the difficulty of isolating dopa or its salts from the acidic hydrolysis mixtures.

VITA

The author was born in Youngstown, Ohio, on January 18, 1918. He was graduated from South High School in Youngstown, Ohio, in January, 1935. He entered Rensselaer Polytechnic Institute in September of 1935 and was granted the Bachelor of Science degree in June, 1939. In the fall of that year he began work in the Graduate School of Rensselaer Polytechnic Institute and was granted the Master of Science degree in June, 1940. During the war years the author was employed as research chemist by Lederle Laboratories, Inc., and by Merck and Co., Inc. He entered the Graduate College of the University of Illinois in March, 1946. There he held a Special Research Assistantship from March, 1946 to August, 1948.



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